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B02

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JAPAN TOBACCO INC

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281/08, 491/048, 495/04, 495/14, 513/14

**HIV inhibitor acting on virus resistant to HIV transcriptase and
protease, useful for increasing latent period before development of
AIDS**

C2004-004744

NOVELTY

An HIV inhibitor contains a tricyclic compound comprising a fused benzene ring; a fused furan, pyrrole, benzene or dihydrobenzene ring; and a fused diazepine, thiazepine, oxazepine or dihydro thiapyran ring.

DETAILED DESCRIPTION

An HIV inhibitor contains a tricyclic compound of formula (I) or its salts.

Ring A = groups of formulae (A-a)-(A-d);

A¹ = 1-6C alkyl, 1-6C hydroxyalkyl, 2-6C alkenyl, phenylalkenyl, haloalkenyl, alkynyl, 2-11C acyl, 3-13C alkoxy carbonylalkyl, carboxyalkyl, or -(CH₂)_n-r¹⁰;

B(6-H, 14-A2B1, 14-L6) .3

r¹⁰ = -CO-N(r¹¹)(r¹²), phenyl (optionally mono or di substituted, by 1-6C alkyl, 1-6C alkoxy, halo, NO₂, CN and/or 5-tetrazolyl) or pyridyl;

r¹¹, r¹², A⁴, A⁵, A⁹, A¹⁰, r⁷⁰, R²³, R²⁴, X²⁰, X²¹ = H or 1-6C alkyl;
Nr¹¹r¹² = piperazin-1-yl (optionally 4-substituted by 1-6C alkyl), pyrrolidin-1-yl, phenyl (substituted by r¹⁴ and r¹⁵) or pyridinyl;

r¹⁴, r¹⁵ = H, 1-6C alkyl, 1-6C alkoxy, halo, nitro, cyano, or tetrazol-5-yl;
n = 1-4;

A² = H, 1-6C alkyl, 2-6C alkenyl, benzyl, 2-11C acyl, acyloxy alkyl, 3-13 alkoxy carbonylalkyl, cyanoalkyl or di(1-6C alkyl)carbamoyl;
A³ = -O-, -S-, or -N(r⁶⁰)-;

r³⁰ = H, 1-6C alkyl, or benzyl (optionally substituted by 1-6C alkyl, 1-6C alkoxy, halo or NO₂;

A⁴-CH-CH-A⁵ = cyclohexane ring;

A⁶ = -S-, -SO-, or -N(r⁶⁰)-;

r⁶⁰ = 1-6C alkyl or 2-6C alkenyl;

A⁷ = -N=N-, -NH-CO-, -CH₂-CH₂-, -O-CO-, -O-CS-, -N=C(r⁷⁰)- or -CH=C(r⁷⁰)-;

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A⁸ = -N-O-r⁸⁰, =N-NH-r⁸¹ or =C-C(=O)-r⁸²;

r⁸⁰ = H, 1-6C alkyl, 2-11C acyl, 3-13C alkoxy carbonylalkyl or 2-7C carbamoyl alkyl;

r⁸¹ = 2-11C acyl or carbamoyl;

r⁸² = 1-6C alkoxy or amino;

R¹, R² = H, halo, 2-11C acyl, COOH, 2-7C alkoxy carbonyl, CN, NO₂, 5-tetrazolyl, -O-R¹⁰, -SO₂-N(R¹⁵)(R¹⁶), -CO-N(R¹⁸)(R¹⁹), -N(R²⁰)(R²¹), -S-R²², or -SO₂-R²⁵;

R¹⁰ = H, 1-6C alkyl, 2-6C alkenyl, -SO₂-R¹¹, -(CH₂)_m-R¹⁴, 2-7C alkyl carbamoyl, di(1-6C alkyl)carbamoyl, 2-7C alkyl amino thiocarbonyl or di(1-6C alkyl)amino thiocarbonyl;

R¹¹ = 1-6C alkyl, or groups of formulae (i)-(iv);

R¹², R¹³ = H, 1-6C alkyl or halo;

R¹⁴ = di(1-6C alkyl)amino, 1-6C alkoxy, 2-7C alkoxy carbonyl, CN, or the residue of 5 or 6 membered heterocycle which contains 1-4 nitrogen atoms;

m = 1-4;

R¹⁵, R¹⁶ = H or 1-6C alkyl (optionally substituted by OH);

NR¹⁵R¹⁶ = piperazin-1-yl (optionally 4-substituted by 1-6C alkyl) or pyrrolidin-1-yl;

R¹⁷ = H or 1-6C alkyl;

R¹⁸, R¹⁹ = H, 1-6C alkyl, or phenyl;

R²⁰, R²¹ = H, 1-6C alkyl, 2-11C acyl, 1-6C alkyl sulfonyl, 2-7C alkoxy carbonyl, or alkenyl carbamoyl;

NR²⁰R²¹ = piperidin-1-yl, maleimide, pyrrol-1-yl, 1,3,4-triazol-1-yl, or a group of formula (v);

R²² = 1-6C alkyl or -CO-N(R²³)(R²⁴);

R²⁵ = 1-6C alkoxy, 1-6C alkyl, 2-6C alkenyl, or benzyl;

X = S, O, -CH₂-CH₂-, -CH=CH-, or -C(X²⁰)(X²¹)-; and provided that, when Ring A is (A-a), A¹ is 1-6C alkyl and A² is H, then R¹ is not H, NO₂, halo, -O-R' or -N(R)(R') (where R', R and R' are each H or 1-6C alkyl).

ACTIVITY

Anti-HIV.

In tests on a clone of HL-60 cells incorporating the HIV-1 gene, (I: R¹ = OMe; A¹ = -CH₂C(Me)=CH₂; A² = Me; X = S) inhibited the increase of HIV-1 p24 antigen with MIC₅₀ of below 80 nM.

MECHANISM OF ACTION

Inhibition of HIV-LTR under HIV-Tat stimulation (HIV-Tat transcription inhibitor).

In tests on cultures of 1A12 cell (The recombinant HeLa cells

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incorporating HIV-LTR promoter) treated with PCMV-Tat plasmid, (I: R¹ = OMe; A¹ = -CH₂C(Me)=CH₂; A² = Me; X = S), expression was inhibited with IC₅₀ below 300 nM.

USE

In mammals, for increasing the latent period between acquiring HIV infection and developing AIDS, useful when virus has acquired resistance to reverse transcriptase or protease.

ADVANTAGE

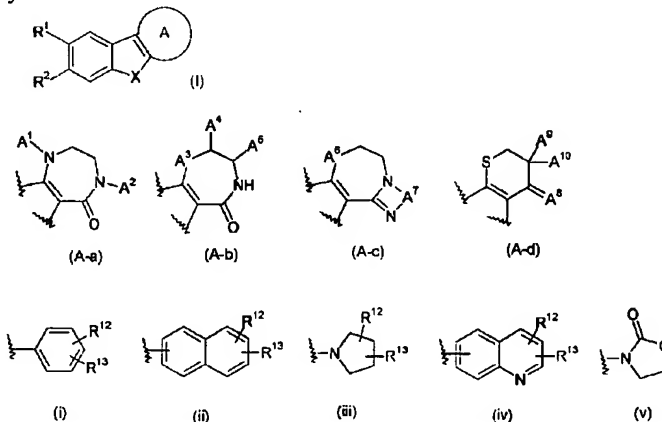
Suppresses HIV proliferation in virus with a different mechanism to antiretroviral (early stage) or protease inhibitor (late stage) drugs, and treatment with it can be given during and after highly active antiretroviral therapy (HAART).

SPECIFIC COMPOUNDS

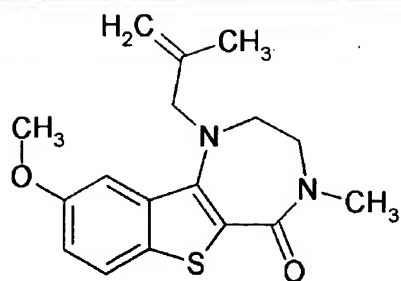
A disclosed compound of (I) is 3-methoxy-8-methyl-5-(2-methyl-allyl)-5,6,7,8-tetrahydro-10-thia-5,8-diaza-benzofazulen-9-one (Ia).

ADMINISTRATION

1 to 1000 mg/kg body-weight once or more/day for an adult, e.g. orally.



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(1a)

(66pp2603DwgNo.0/0)

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